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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 10/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/085,783	LIEW ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58,60,66,68 and 73-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58,60,66,68 and 73-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. It is noted that applicant has filed claims to a different invention than was originally elected. Namely, the instant claims require the detection of transcripts to only three of the originally elected set of ten genes. The examiner has agreed to examine these amended claims.

2. Claims 58, 60, 66, 68, 73, 74, 75, and 76 are pending. Applicants' amendments, remarks and declaration have been carefully considered but are not persuasive to place the claims in condition for allowance for the reasons included in this office action. **This action is FINAL.**

Compact Disc Submission

3. The specification is objected to because the incorporation by reference of the compact disc is not proper. The amendment filed 12/16/05 amends or adds a compact disc(s). See 37 CFR 1.77(b)(4) and 1.52(e)(5), and amends the specification to refer to the compact discs. However, the discs were reviewed by PTO staff and it was found that copy 1 and copy 2 of the discs were not the same. Applicant is required to resubmit identical discs with proper accompanying papers.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 58, 60, 66, 68, 73, 74, 75, and 76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Invention

Each of the rejected claims is drawn to a method for diagnosing osteoarthritis, mild osteoarthritis, moderate osteoarthritis, marked osteoarthritis, or severe osteoarthritis. The claims all recite a method step of "determining the level" of "RNA transcripts of each of Tumour Necrosis Factor Alpha-induced protein (TNFAIP6), Calmodulin 1 (CALM1), and Laminin, gamma 1 (LAMC1) in a sample from an individual suspected of having or being afflicted with" the particular level of OA recited in the claims. Claims 58, 60, and 66 conclude by stating that the detection of differential expression is "indicative of the disease," referring to "the disease" osteoarthritis, mild OA, and severe OA in these claims respectively. The specification teaches that "indicative of disease" refers to "an expression pattern which is diagnostic of disease such that the expression pattern is found significantly more often in patients with a disease than without the disease (p. 27, final ¶)." Thus, for the practice of these claims, one must be able to reliably predict that the expression pattern detected in the claims is found more often in patients with disease than without. Claims 68 and 73 depend from these claims and has a further method step of isolating RNA from said cartilage sample.

Claims 74, 75, and 76 conclude that the comparison of expression pattern derived from a suspected individual against the pattern from "one or more control individuals results in a determination that said individual has" OA, mild OA, or sever OA. Thus these claims differ from the first set of independent claims because they require a definite conclusion that the tested individual has the disease, and in fact the plain language of the claim encompasses drawing this

conclusion simply based on the fact that the comparison was made, regardless of the nature of the result of the comparison. Thus, the nature of the claimed invention requires the knowledge of an association between the gene expression of the three elected genes and osteoarthritis, or some stage of osteoarthritis as recited in the claims. The practice of the claimed invention for the "diagnosing" OA or the staging of OA requires for claims 74, 75, and 76 requires the knowledge that not only are genes differentially expressed in OA, but also that this expression is specific to OA or a stage of OA in such a way that one can reliably draw conclusions for the diagnosis of OA based on the gene expression patterns.

Scope of the invention

The rejected claims include claims for diagnosing all OA, and also for diagnosing different stages of OA (mild or sever OA). The claims recite "determining the level" of RNA transcripts "in a cartilage sample." The claims are sufficiently broad so as to encompass the comparison of a single test individual against a single control individual, and the claims set forth that ANY difference of expression, in any direction (i.e. upregulation OR downregulation) for each of the three recited transcripts would be sufficient to make a conclusion regarding the indication of disease or the presence of disease, and more particularly the claims encompass the staging of OA as mild or severe based on the expression of these three genes.

Guidance in the specification and Working examples

The specification teaches that "'diagnosis' refers to a process of determining if an individual is afflicted with a disease or ailment (p. 19, lines 9-10)." The specification does not provide a single working example where the claimed method is actually practiced for the diagnosis or staging of OA in a patient, human or otherwise. The specification provides an

experimental section with "examples," but these are not examples of the instant method being used.

The examples in the specification which were used in the production of Figure 6 involved the isolation and sequencing of ESTs from fetal, normal, mild, and severe subjects with osteoarthritis. Example 1 teaches the extraction of RNA and cDNA library construction from fetal cartilage. The specification does not provide any details as to the number of individuals whose cartilage is represented in the sample, and so the presumption is that the library represents the RNA of a single individual. A total of 13,398 sequences were obtained and sequenced from the library, of which 5,747 matched to known genes (specification p. 74). Example 2 teaches a similar extraction and sequencing of a cDNA library from "normal adult cartilage." Like in example 1, the specification does not provide any details as to the number of individuals whose cartilage is represented in the sample, and so, the presumption is that the library represents the RNA of a single individual. A total of 17,151 sequences were obtained and sequenced from the library, of which 6,755 matched to known genes (specification p. 75). Example 3 teaches a similar extraction and sequencing of a cDNA library from "mild osteoarthritic cartilage" and "severe osteoarthritic cartilage." Similar to the previous examples, the specification does not provide any details as to the number of individuals whose cartilage is represented in the samples, and so, the presumption is that the libraries represent the RNA of a single individual. A total of 12,651 and 14,222 sequences were obtained and sequenced from the mild and severe libraries, respectively, of which 43% and 51% matched to known genes (specification p. 77).

Example 4 states that genes that are differentially expressed between the libraries are identified through "relative EST frequency analysis," and the results are given in figure 6.

Turning to figure 6, and referring specifically to the elected invention, data is given for each of the elected genes. The strongest relative differences were observed for calmodulin 1 (CALM1). Expressed sequence tags (EST) from this gene represented 0.13% of the transcripts for normal, 0.25% for mild and 0.32% for severe OA samples. However, before reliable conclusions can be drawn in the diagnosis or staging of OA using just this gene or a group of genes comprising this gene as an indicator, there are many unresolved issues. First, given the small sample size, it is not clear that these data are representative of any population or of simply of differences between individuals. No statistical analysis is given. For example, the relative expression is increased in severe OA versus mild OA but it is increased in normal versus both of these. It is not clear from the specification what level of difference in expression is diagnostic of OA or a stage of OA. It is not clear that the test itself of "relative EST frequency" is valid given that the total pool of EST tested in each sample is different. The changes in "relative frequency" could be a result of differences in expression levels of other genes that cause the total number of expressed genes to increase or decrease relative to the gene in question. Almost every single gene that displayed appreciable expression in these libraries did so at different relative levels.

The data presented for the remaining genes in this group represents very low transcript numbers. The LAMC1 gene was detected only in fetal and normal cases with no expression in OA patients. Does this mean that the absence expression of LAMC1 in a patient is diagnostic of OA? Likewise, the TNFAIP6 gene was detected only in mild and severe OA, but not in normal or fetal libraries. Does this mean that if TNFAIP6 is present in a sample the individual has OA, and if so, is it mild or severe or both? The CALM1 gene shows a clear increasing progression from normal cartilage to severe, but there is no indication in the specification as to what level of

expression would in fact be indicative of any of the phenotypes which are diagnosed by the instant claims.

The some of the claims specifically recite detecting moderate or marked oseteoarthritis, but no data is given with regard to these stages. The claims are drawn to using a combination of genes for the diagnosis of OA or different stages of OA, yet the specification does not provide any guidance or discussion as to which expression patterns of the elected genes are diagnostic of disease or stages of the disease. The implication of the claims is that some diagnostic pattern of expression might be obtained by testing for the expression of the three elected genes. However, the specification does not provide any guidance as to what this pattern is, how the expression of the different genes relates to the positive diagnosis of OA or any particular stage of OA as recited in the claims. The specification does not provide any guidance as to how one should proceed, for example, if a patient is tested and exemplifies down regulation of TNFAIP6 and LAMC1, and up regulation of CALM1 relative to a "normal" control.

Teachings in the Prior Art, Level of Unpredictability

The state of the art is highly unpredictable. It is impossible to predict, a priori, which gene transcript pattern would be diagnostic of OA, or even given data in the specification if there are any patterns that might be relevant for the three elected genes and OA in general or for the different stages of OA. Particularly, in order to diagnose the different stages one would have to extrapolate from the data given what patterns might be used to indicate the presence of disease.

Quantity of Experimentation

The experimentation necessary to practice this invention would be enormous, if it were possible since this is such a highly unpredictable area. Given the data in the specification, one

would have to first undertake experimentation to confirm that in fact the genes in the elected group are differentially expressed in normal patients versus those with OA, and versus those patients having of the specifically recited stages of OA. All of this experimentation would have to be replicated in order to ensure that the relationships developed and the putative expression patterns are in fact sufficient to draw conclusions that OA or particular stages of OA are present, as recited in the claims.

Conclusion

Thus, given the unpredictability in this art area, given the lack of working examples and guidance in the specification, given the breadth of the claims and the nature of the invention, it is concluded that it would require undue experimentation in order to practice the claimed invention.

Response to Remarks

Applicant's remarks have been considered but are not sufficient to overcome the 112 1st paragraph rejection.

First, regarding the nature of the invention, applicant states that "the use of EST frequency to draw conclusions regarding differential expression is a scientifically acceptable technique (remarks filed 7/17/06, p. 17)." Applicant refers to references by Okubo et al., Kumar et al., and Dahl et al. as evidence of this position. The Okubo et al. and Dahl et al. references do not appear to be part of the current file wrapper. The Kumar et al. reference was included in an IDS filed 8/27/02. Kumar et al. undertake a similar study to that set forth in the instant application. In their discussion, they discuss transcripts which were present at very low levels in samples, such as those "represented by only a few or often by a single EST." Kumar et al. state "It is not clear is such low level of expression is functionally relevant (p. 650, 1st column) and go

on to state that "To begin to understand function, the expression pattern of these genes first needs to be compared using additional approaches such as Northern blotting and in situ hybridization. If confirmed, further evaluation of patterns by quantitative and biochemical analyses would be required (bridging p. 650-651)." Thus, Kumar et al., while using a similar technique, caution against being overreaching regarding conclusions, especially regarding low abundance transcripts. In the instant case, the three genes whose transcripts are required by the claims are all represented at very low levels in the tested libraries. Applicant's declaration is discussed later in this office action.

The amendments to the claims significantly narrow the scope of the claims with regard to they type of sample tested (to cartilage) and with regard to the fact that the detection is of human OA. The scope of the claim remains quite broad with regard to the fact that the comparisons in the claims encompass the detection of only one individual versus another individual, and further with regard to the fact that the claims set forth that any difference in expression levels or any comparison of patterns is sufficient to draw conclusions regarding the indication of OA, mild OA, or sever OA, or regarding the presence of one of these.

Applicant returns to the argument that EST frequency data is a acceptable technique for drawing conclusions regarding differential expression data, and applicant states in the remarks (at page 19) and in the declaration that the libraries created in the examples in the instant specification were constructed from pooled mRNA from different individuals. Kumar et al. also speak to this aspect of the technique teaching that "significant patient to patient variation in the expression pattern of any one gene may be masked" due to the pooling. This simply underscores the fact that the data provided in the instant specification would require further confirmation and

analysis to confirm that reliable conclusions can be drawn based on the expression of the three genes recited in the claims.

The instant situation differs tremendously from In re Angstadt, wherein a large number (forty) examples were provided, only one of which did not work. In In re Angstadt, the court determined that there was sufficient guidance in an unpredictable art. The court further stated, however, that "each case must be determined by its own facts." The facts of this case do not support an enabled use for the claims, for all of the reasons discussed in the rejection. Here, the situation is quite different because the specification does not provide data or guidance sufficient to support the claims of any embodiment of the claimed invention, let alone multiple embodiments.

Applicant continues on page 19 with discussion of the declaration filed 7/17/06. The showings of the declaration clearly support the assertion that these three genes are differentially regulated in patients with OA versus those without OA, namely that there is up regulation in the case of TNFAIP6 and CALM1 and down regulation in LAMC1. However, these showings are not commensurate in scope with the claims and/or not sufficient to overcome the rejection for at least the following reasons:

(A) These results are based on the comparison of populations of people, OA patients versus healthy patients. The instant claims are sufficiently broad so as to encompass the detection of a test individual to a single control individual. Neither the claims, the declaration nor the specification set forth any guidance for any of the three genes as to what difference, when a single individual's test sample is compared to another individual's expression level or even to

some population average, would be sufficient to make a conclusion concerning the presence or absence of OA, and particularly mild or severe OA.

(B) The declaration provides a conclusion of up regulation or down regulation for each particular gene. The claims are sufficiently broad such that any difference observed for each gene would be sufficient to draw a conclusion that disease is present.

(C) The declaration provides statistical analysis of only the difference between OA and normal test samples. Many of the instant claims set forth concluding that "mild" or "severe" OA are present, in particular. There remains no guidance in the specification as to how to drawn this conclusion.

(D) The declaration does not show that either up regulation or down regulation relative to a control population for all three of these genes is sufficient to draw a conclusion regarding the definitive presence of disease, as set forth in claims 74, 75, and 76. The claims are sufficiently broad so as to encompass that any change relative to any control is sufficient to conclude an indication or presence of disease. No guidance in the specification provides how to use any profile for these three genes to draw a such a robust conclusion as is set forth by the plain language of these claims.

On page 20 of the remarks applicant makes a note that the data obtained for B2M, ZFR, and TCTP by hybridization does not support the EST frequency data. As these genes have been removed from the claims, and as the claims recite particular combinations, these remarks are not relevant to the instantly claimed invention.

Applicant points out that the specification teaches the use of genes of the invention for diagnosis, citing page 21 of the specification. However, this discussion is not on page 21 of the

specification. There is discussion on page 64 of "Diagnostic or Prognostic Tests," however, this discussion is general in nature and does not address the enablement of the specifically claimed invention. This general discussion was considered in the rejection, and the is not sufficient to overcome the lack of enablement regarding the specifically elected combination of genes. Likewise, example 9 (on p. 84 of the specification) is prophetic in nature and is not a working example. Furthermore, applicant discusses that a "expression pattern" is indicative of disease if it is found "significantly more often in patients with disease than in patients without the disease using standard routine statistical methods." However, the specification does not provide an example of an "expression pattern" containing the three elected genes that has been determined "using routine statistical methods" to be present more often in patients with disease than without disease. Though the declaration begins to provide the relevant data to support such an assertion, the declaration is not sufficient for the reasons discussed previously in this office action.

The comments regarding whether changes in gene expression might be a generalized response or particular to OA are persuasive insofar as the claims have been limited to the testing of cartilage samples (see remarks p. 21). However, it is noted that the declaration does not provide any data regarding the how to use the genes set forth in the instant claims to differentiate between stages of OA.

Applicant's final comments on page 23 of the response state that diagnosis is not performed in the absence of other medical information, and that other tests and factors are often used in diagnosis. However the plain language of the instant claims, particularly claims 74, 75, and 76 end with a "wherein" statement that concludes that "said individual has OA" or the particular stage of OA. While one might argue that claims 58, 60, 66, and 68 allow for some

"other tests" since they lead only to a conclusion that differential expression is "indicative of the disease," one cannot ignore the plain claim language of claims 74, 75, and 76.

The rejection is maintained and modified for the amended claims.

Conclusion

6. No claim is allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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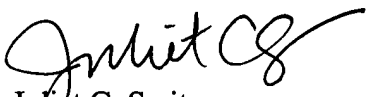

Juliet C. Switzer
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Art Unit 1634

September 25, 2006